Biomedical Education with Golem

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Abstract. This article gives a review of the use of simulation models in medicine and physiology. It also explains our concept of work in this area, which has lead to the elaboration of a multimedia medical simulator called GOLEM. Physiological models are spreading fast in today's medicine. They can, for instance, help to govern modern medical machines. Small lumped parameter models can be used in clinical practice to help physicians with diagnostics and to propose possible treatment. Large-scale models cannot generally be identified to the state of a particular patient, but they have been used to solve conceptual problems in physiology (e.g. the influence of a weightless state on a function of human circulation, respiration and other physiological subsystems). Recently, we have experienced an increased effort to put the large-scale models to use in multimedia education programs, such as GOLEM.

Models and Medicine

Just as the wise, old Rabbi Yehuda Loew of Prague brought life into a pile of mud, an elaborated simulation model of physiological processes brings functionality into a medical educational simulator. Such a simulator then enables medical students and doctors to "get in touch" with the given problem in virtual reality. Simulation games give the opportunity to test the behavior of the simulated object without any risk; to diagnose and treat a virtual patient.

A model can underlie the evaluation of measured clinical and physiological data in modern medical diagnostics. Simulation calculations govern modern dialyzing machines and help divers follow a safe mode of surfacing (decompression).

Evolution of modeling in biology and medicine is closely connected with mathematically formalized description of biological reality – i.e. the transformation of a purely verbal description of a given network of relations into a description in the formalized language of mathematics. Biological and medical sciences share, in contrast to technical sciences, physics or chemistry, a common handicap. The process of formalization in physics was begun in the 17th century. However, it was much delayed in the medical and biological sciences, owing to the complexity of the studied systems. We have only made the major breakthrough in this area with the use of cybernetics and computer technology.

Formalized description of the physiological reality starts with the pioneering work of Grodins et al. [1] in the end of 1960's. A classical milestone was a description of circulation by Guyton et al. [2], [3], [4] the first large-scale model, which attempted to cover in broader perspective the physiological interconnections between circulation, breathing and kidneys.

The next wave of formalization of physiological systems has only started in recent years, brought forth by the new possibilities introduced by technical progress in the area of computer science and the Internet. The number of studies that use computer models for *evaluation and interpretation of experimental data* (particularly when studying nervous tissue, respiration, circulation and kidneys) is steadily increasing.

In the same way as theoretical physics tries to formally describe physical reality and explain the experimental data, theoretical biology and physiology tries to create a formal description of the intricate relations in living organism and explain the quantitative data of experimental workers.

Project Physiome

The new *international project PHYSIOME* (http://physiome.org) tries to concentrate the activities in this area. It is a successor of the successful project *GENOME*, whose goal was to map the DNA sequence of human genome. The goal of the project *PHYSIOME* is to integrate the current biophysical, biochemical and physiological knowledge using formalized description and the respective model of a physiological system.

Small Lumped Parameter Models for Practical Use

Simpler small lumped parameter models can be put to use in clinical medicine. The parameters can be identified with the physiological values of patients and used for diagnostics and proposition (and possible management) of the therapy. This is why there is the demand for use of the so called minimal models in the literature. Their parameters, acquired by identification of the model to the measured data of the patient, have an explicit meaning that is clearly understood by clinicians. As an example, let's name the minimal model of the glucose metabolism [5], [6] or a minimal model of circulatory system, which has been successfully used in clinical practice at the Institute of Cardiosurgery of A.N. Bacoulev in Moscow [7].

Large Models – Problems with Identification

However, a living organism is far too complex an entity to allow a description of all its behavior by a small simple model. Since the end of the 1970's, large scale models have been appearing in the scientific literature. They attempt to cover and integrate the intricate relations between the kidney regulation, breathing, circulation, ionic composition of bodily fluids and their acid-base chemistry while using non-linear differential equations (Guyton et. al [3], [4], Ikeda et al. [8]). These models have often more than a hundred variables and more then hundred other parameters. Such a number of variables are impossible to measure at once in one particular individual, let alone to identify the model from their values. Besides, some physiological values in man can only be measured indirectly or even just estimated (e.g. total content of ions in the cells).

This is why these large scale models issue from the data assessed in experiments with individual isolated subsystems. For example, we start from the experiments which assessed the behavior of blood samples (with different concentrations of hemoglobin) when titrated by a strong acid or a strong base and subsequently equilibrated with different concentrations of oxygen and carbon dioxide. In this way we obtain the subsystem of blood, which is then interconnected with other subsystems of a large-scale model (respiratory, circulatory, kidney, hemopoetic etc.) and with the pertinent regulation circuits. This enables us to model for instance the consequences which either respiratory insufficiency or various modes of artificial ventilation have on acid-base chemistry and blood gases transport in the organism as a whole.

Time courses of individual measurable variables in certain physiological and pathological situations are compared for the sake of identification of large-scale models. A number of things were ignored or simplified even during elaboration of a large-scale model. Thus, the criterion for the sufficient correspondence of the large-scale model with the behavior of the physiological original is not the exact match of the model's predicted variables to the data of the particular patient, but rather a match in the time courses and the progression of their values. This should be achieved in various modeled situations.

Good Knowledge of Physiology Is a Precondition

The necessary base for the successful elaboration of a large-scale model is its suitable hierarchical organization into individual subsystems. A model must be well balanced – regulation links must be in same hierarchical level; we must consider well about what can and what cannot be ignored at each hierarchical level. The elaboration of a model is an art of its own, naturally one that is based on a solid knowledge of physiology. An example of a sound structuralization is the already mentioned model of Guyton at al. [2], [3], [4], whose further elaboration lead to the model "Human" (Coleman et al. [9]) or the model of Ikeda et al. [8]. On the other hand, examples of unsuitable model hierarchy (which result in not completely adequate model behavior) can be given as well - in 1979, a group of Ukrainian authors under the leadership of N. Amosov published the results of their creating of an extensive physiological regulation model [10]. Their model comprised of several interconnected subsystems (circulation, respiration, volume and ionic homeostasis, thermoregulation etc.). The behavior of the model was rather unsatisfactory in some cases and thence apparently came the later considerable skepticism of Amosov towards large-scale physiological models. The source of the inadequate behavior was in the ignoring of some basis regulatory links - e.g. the influence of aldosterone on excretion of potassium, underestimation of the relevance of the acid-base regulation to the blood gases transport etc. However, we don't have to go far in history to find examples of bad structuralization. An extensive model, created for the needs of NASA, was published recently (Murphy, Coolahan et al. [11], [12],[13]) The authors interconnect several models originally created by different workers into one complex implemented on several parallelly operating computers (circulatory system, model of heart ventricles, respiratory subsystem, subsystem of muscle work – synthesis of lactate etc.). The authors seem to have been fixed on the resolution of problems regarding parallelization of the demanding computations rather then actual elaboration of the physiological model. The resulting model behavior did not correspond with the exerted effort.

When connecting various subsystems, it is necessary to have in mind not only structural, but also temporal aspects – various physiological regulations take various times to exert an effect. An example of a model with well interconnected subsystems that respected time aspects was an extensive model of physiological regulations that was being elaborated by NASA for the purpose of space physiology research (Fig. 1).

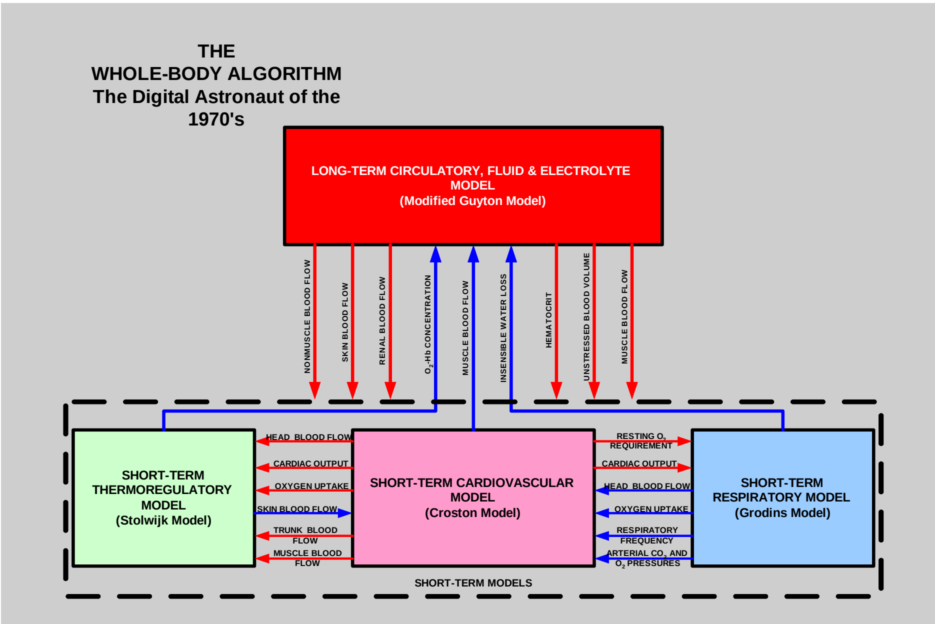

Fig. 1. Structure of the large-scale model of physiological functions from NASA

Nonlinearity and Stability, Stiff Equations

Physiological systems are characterized by a number of nonlinearities. Regulation links exert their effects in different time frames. This quite often leads to stiff equations. An important feature of these nonlinear systems is their admirable stability. It is interesting that when we ignore some important regulation links or their time frames, it can result in instability. For instance, acid – base chemistry is regulated on several levels: Chemical level based on buffering reactions (in order of milliseconds), transport of ions between blood and interstice (in order of minutes), transports of ions between a cell and interstice (in order of hours), regulatory response of respiration (6 – 12 hours) and regulatory response of kidneys (3 – 5 days). If we set the parameters of the model to respond faster then naturally to a disequilibrating stimulus, then the adaptor response can easily take the system into oscillation and instability.

Large-Scale Models Used for Resolution of Conceptual Problems

Large-scale models are important for integration of our physiological knowledge (of individual physiological subsystems) into the picture of the entire organism. That is why the term “integrative physiology” is sometimes used for this area of physiology. Hence, the goal of their creating is first of all resolution of conceptual physiological problems. Models can be used to observe the causal chain of events during development of various pathological states and thus clarify the importance of various regulatory circuits in etiology and subsequent therapy of various diseases.

For instance, the extensive model of the circulatory system by Guyton et al. helped to clarify the relations between the volume of bodily fluids and the circulatory system regulation. Extensive models were used during space research projects. They wanted to resolve the conceptual questions concerned with the effect of the weightless state on the human organism. In the 1970’s and 1980’s, the team of Guyton et al. occupied their minds with these problems within the project “*Digital Astronauts*” (White [14]) in the USA, while the team of Verigo et al.. did similar research in the former USSR. We are currently experiencing a renaissance of these approaches in the framework of a new international project “Digital Astronaut”, as there is a renewed interest in the questions around the long term stay of astronauts in a weightless environment.

However, large-scale models of physiological systems do not only have a theoretical significance. They are also a powerful means of education – integrated into an interactive multimedia milieu of educational programs, they can demonstrate complex regulatory processes (and their disorders) in a friendly form of a simulation game. The output of the model can be visualized by numbers, graphs, change or movement of animated figures, etc. This can be a perfect combination to explain causal relationships and time course of complex processes. Thus, medical and biological computer models are now finding their direct use in sophisticated educational programs and medical simulators. Their importance is going to increase even more with the widespread utilization of computers and the Internet.

Before and Now – Shared Knowledge vs. Company Know-How

The possibility of commercial use of the models has brought about a different view on the formalized description of physiological systems. Description can serve as the basis of an educational simulation model. Therefore, a detailed formalized description (in the form of equations or, even better, algorithms described by a source code in a common programming language), which used to be of *scientific interest* only, has

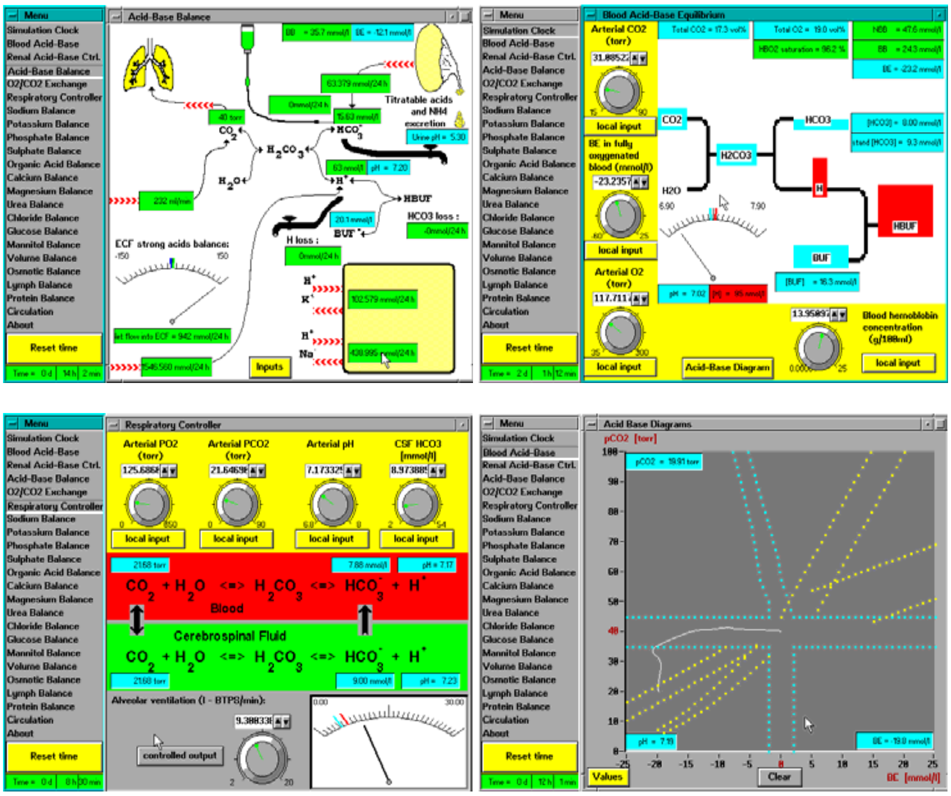

Fig. 2. Panels of acid-base balance in Golem simulator

become *technological know-how*. As late as at the end of 1980's, it was still usual to receive a printout of the particular Fortran code outright upon a written request to the authors. Currently, this is not a common practice anymore. For instance, the theoretical basis upon which the models of the American firm Critical Concepts (a producer of medical simulators, http://www.critcon.com) are built is not specified, except for very general information.

As our workgroup has been engaged in the problems of biomedical system simulation since the mid-1970's, we have perceived the current situation as an intellectual challenge. We wanted to have been creating multimedia educational programs that would not be just animated pictures combined with hypertext, but rather those permitting, in addition, various simulation games. Thus, we couldn't but to get to work on the formalization of the global physiologic regulation and we started off creating complex simulation models of interconnected physiological systems by our own means.

The outcome of our work is the medical simulator *GOLEM* (Kofranek et al. [16], [17]), at whose basis is an extensive model of global physiological processes, including respiration, circulation, kidney function, ionic, volume and acid-base homeostasis, as well as the influence of regulatory hormones (see Fig. 2). The model

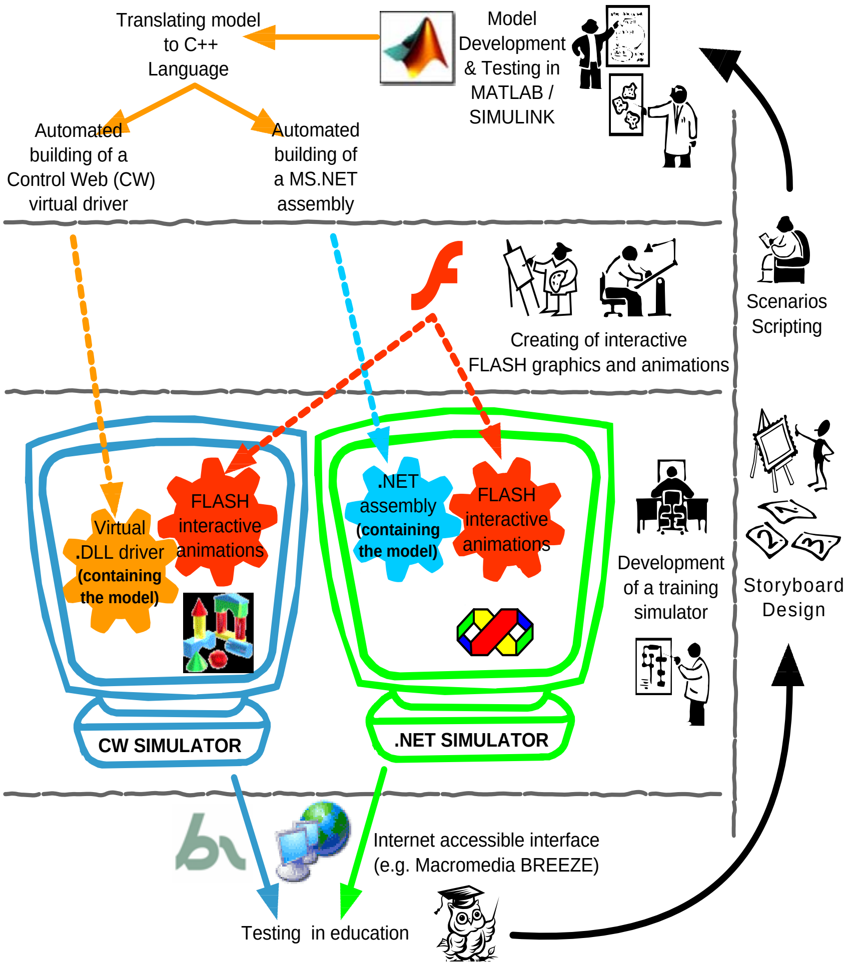

Fig. 3. The development cycle of educational software

comprises of 38 nonlinear differential equations and more then 200 variables (parameters). Its current structure is presented at http://www.physiome.cz .

The model enables us to demonstrate various combined disorders of internal environment, respiration and circulation, together with various effects of therapeutical interventions.

Our teaching experience points out a feature of the simulator that proves to be an advantage. It is the possibility of disconnecting the individual subsystems from their neighboring subsystems, which gives students the opportunity to study their behavior when separate. Such a use of the simulator makes students understand better the dynamics of the complex regulatory loops in the organism, as well as their exertion during various pathological states.

Besides further elaboration of *GOLEM*, we currently create specialized multimedia educational programs concerned with normal, pathological and clinical physiology of respiration, internal environment, kidneys and circulation. We try to make a substantial use of simulation games (Kofranek et at. [18], [19]).

The simulators of the physiology of man can be, of course, used for other means than educational. We prefer, however, the educational and medical use to the other possibilities (such as elaboration of a “digital soldier” [23]).

Educational Software Design

Just as the reception of a text-book by students depends on the author’s ability to explain complex material in an illustrative and comprehensive way, the key to success of multimedia educational software is a good scenario. Thus the ***design cycle*** of our programs (see Fig 3) begins with the creation of scenarios. A scenario comprises not only textual material, but also of the cartoon strips of the “storyboard” which will later help the graphic designers create graphics and animations. More professionals are involved in the development cycle besides the already mentioned graphic designers and physiology teachers (responsible for the scenario).

Construction of a simulation model is truly in the domain of science. There has to be established cooperation among system engineers (skilled in mathematical modeling), physiologists and eventually physicians (if the model is supposed to be applied in clinical medicine) on this level. The next level of an educational software elaboration is more likely an industrial work. It consists of wrapping the simulation models with graphical user interfaces according to the scenario and is done by application programmers and web designers (see Fig. 4). Last but not least, the software enters the testing phase in the education process. Further refinements are made, if required by the teachers.

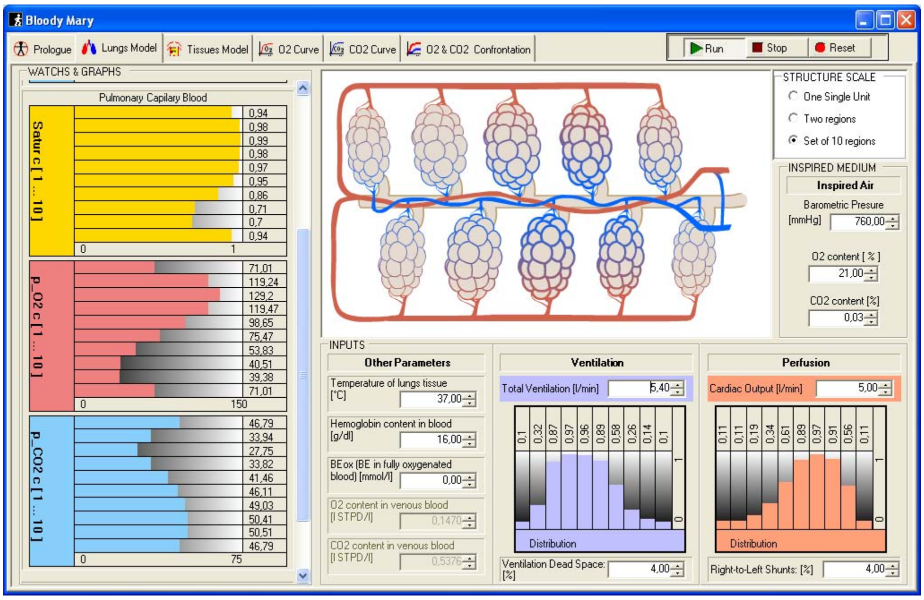

Fig. 4. An example of a simulator user interface combining custom MS .NET controls (bar graphs) with Flash animations (alveoli)

Conclusion

The creation of modern educational software is a challenging and complicated project requiring the team cooperation of various professionals:

- *Skilled teacher / physiologist* - who prepares the scenario (including the basic design of pictures and interactive animations) and tests the final products as a teaching aid.
- *System analyst* – an expert that designs, formalizes and tunes the simulation models in cooperation with a physiologist. The means of their mutual communication are the simulation chips in the Matlab/Simulink environment.
- *Graphic designer* - designs and constructs graphical components for simulator user interfaces and produces interactive animations in Macromedia Flash.
- *Application* p*rogrammer / Web designer* - utilizes Microsoft .NET or Control Web as a container for the simulation model. He/she connects it with the interactive animations, and other multimedia features, and programs the actual educational application.
- And the *student,* of course, for whom the whole product is intended and whose comments when testing the program are of high interest to the teacher and the developers.

It is clear that *convenient developer tools and a sound design methodology save time and money*. We have chosen different specialized tools for the different types of tasks and it has proved to be a great advantage. We use Simulink (by MathWorks) for the development of simulation models, Stateflow (by MathWorks) for the visual description of the interactive scenario (in the form of statecharts), Macromedia Flash for the design of the interactive animation components and Microsoft Visual Studio .NET or Control Web for the development of the final form of the educational program.

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